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I. Tumours of the lung

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Lung tumours are not common in domestic animals; there has not been the increase in epidermoid carcinomas and anaplastic small-cell carcinomas that has occurred in man this century. Adenocarcinoma is the most common type in animals. The biological behaviour of each type of tumour in animals seems to be much the same as in man. The tumours are described histologically, the main categories being: epidermoid carcinoma, anaplastic carcinoma, adenocarcinoma, combined epidermoid and adenocarcinoma, carcinoid tumours, bronchial gland tumours, benign tumours, and sarcomas.

The tremendous increase in the frequency of lung cancer in man, which is mainly due to a rise in the number of cases of epidermoid carcinoma and anaplastic small cell carcinoma, raises the question of the incidence and nature of lung tumours in animals. Domestic animals share man's environment; they breathe the same polluted air and some of them—particularly the pet dog and cat—eat similar food, mostly prepared on an industrial basis. Study of the incidence, behaviour, and histology of naturally occurring lung tumours of animals may shed some light on the epidemiology and etiology of pulmonary neoplasms in man and may facilitate the interpretation of some of the observations in experimentally induced lung tumours in animals.

In the veterinary literature, there are only a few comprehensive papers on primary lung tumours in domestic animals. According to Nielsen (1), some 200 canine and only about 40 feline cases of undoubted primary lung carcinoma have been recorded in the literature. This neoplastic condition is very uncommon in farm animals, since, for economic reasons, these animals are usually not allowed to live their whole life span. The slaughter of such animals in adolescence or early maturity may be the reason why the literature on oncology in swine, ruminants, and horses is so scanty. Most of the statistics on animal tumours are therefore limited to dogs and cats. In sheep, however, there is a particular neoplastic condition, which has been studied to some extent in the last decade. This lung neoplasm, which produces severe dyspnoea, is called *jaagziekte* or lung adenomatosis (see page 18).

A statistical analysis has to take into account the fact that the average life span of dogs has doubled during the last 15–20 years. For some years neoplasms have represented the predominant cause of death in dogs submitted for necropsy in Zurich. The average age of such dogs increased from 3.8 years in 1953 to 7.8 years in 1970. It is not surprising, therefore, that many more tumours are seen in the autopsy room than was the case 10 or 20 years ago.

In Zurich, during the last 25 years, we have encountered 84 primary lung tumours in dogs (0.9% of the total number of dogs necropsied) and 57 cases in cats (0.5%). In that period, we also had an opportunity of investigating 12 bovine and 8 ovine pulmonary carcinomas. Those numbers are certainly modest. The scarcity of the material should therefore be taken into account when interpreting some of the statistical data. With the assistance of WHO, we obtained 196 additional canine and 15 feline cases from 9 departments of veterinary pathology in 5 countries. The total numbers of cases—280 in dogs and 72 in cats—give some information on the relevant frequency of the tumour types. The incidence and distribution according to sex and breed could not be investigated because data on the dog and cat populations of the countries in question were not available.

In many of the old statistics, primary and secondary lung tumours were not distinguished with sufficient accuracy. This distinction may indeed be difficult, especially in cases where only some organs

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were submitted by the practitioner. Occasionally we have necropsied bitches that had previously had a mammary gland tumour removed surgically. In those cases it was sometimes difficult to distinguish between a primary pulmonary adenocarcinoma and a late metastasis of a mammary gland tumour. Such debatable cases have not been included in our material.

A classification of lung tumours in man may be based on strictly histological criteria, histogenesis, or clinical behaviour; in animals, there is no alternative to basing it on strictly histological aspects. The final goal of a classification of animal lung tumours is to provide data that may be of value for comparative pathology. The system proposed by WHO (2) for typing lung tumours in man has therefore been used as the principal guideline for our system. In some cases where histogenetic, clinical, or epidemiological factors may have influenced that system our classification has had to be limited to purely histological criteria, since clinical experience, the prognosis of surgical treatment, and epidemiological data on animal lung tumours were lacking. Some differences between the classifications of lung tumours in man and in animals have therefore been necessary.

In many instances different histological types were observed in the same tumour, so several areas had to be investigated in each case. An adenocarcinoma may consist partly of columnar and partly of cuboidal tumour cells. In these cases the diagnosis should be " columnar partly cuboidal cell adenocarcinoma ".

The tumours should be graded as highly, moderately, or poorly differentiated. A neoplasm that shows no differentiation is designated as an undifferentiated or anaplastic tumour. A loss of differentiation means a change of the cytological characteristics or of the architectural characteristics of the tissue of origin of the neoplasm. In man and animals the degree of differentiation is used as a measure of malignancy.

Occasionally a tumour is found to be composed of tumour tissue with two different kinds of differentiation—for example, small cell anaplastic carcinoma (mostly of fusiform type) may show some areas of adenocarcinomatous formation or some epidermoid islets. The more highly differentiated type of cells will be used for classifying such tumours, e.g., " epidermoid carcinoma, partly undifferentiated " or " adenocarcinoma with anaplastic or undifferentiated areas ". The nomenclature problems involved in these uncommon tumours have been discussed by Kreyberg et al. (2) and Kreyberg (3).

Very rarely, a tumour may consist of two neoplastic tissue types of equal differentiation. The term " combined tumour " is then appropriate. In lung tumours, an adenocarcinoma may show some islets of epidermoid differentiation. According to Kreyberg (3) such a tumour should be named " combined tumour ", provided that the two tumour types are equally represented. In contrast, a " pulmonary mixed tumour " shows a combination of a mesenchymal tumour part and an epithelial neoplastic proliferation.

Regarding the malignancy of the various tumour types encountered in animals, the situation seems to be very similar to that observed in man. In animals that died from lung cancer, metastases were usually observed, predominantly in the bronchial lymph nodes. In cases where the tumour had spread from the lungs *via* the blood stream, we found metastases in the brain and other organs. Intrapulmonary metastases spread *via* the air ways are common in adenocarcinoma, where often several lung lobes may show disseminated foci of tumour tissue. In some instances, spread to the adjacent pleura and pericardium were observed. When comparing the behaviour of lung tumours in animals with those in man, it has to be taken into account that euthanasia may be carried out before metastases have had time to develop. We are not in a position, therefore, to give any statistical data regarding the frequency and localization of metastases, as some 40% of our dogs and cats were killed owing to severe loss of condition.

The average age of the dogs suffering from lung carcinoma was 11.4 years and the corresponding age of cats was approximately 13 years. The canine

Table 1. Prevalence of different types of tumour in man, dogs, and cats

Main type of tumour	Man [a] %	Man [b] %	Dog [c] %	Cat [c] %
epidermoid tumours	40.9	38.2	6	5
anaplastic tumours	40.4	40.4	8	—
adenocarcinoma	13.7	7.1	83	87
other lung tumours	4.9	14.2	3	8

[a] Kreyberg (3).
[b] Eck et al. (4).
[c] Observations in Zurich.

anaplastic carcinoma is a tumour of the younger age group (average age: 7.5 years), as it is in man, whereas adenocarcinoma affects older dogs (average age: 11.5 years).

In domestic animals, adenocarcinoma is undoubtedly the most prevalent type of cancer, whereas epidermoid and anaplastic carcinoma are rare in the dog and anaplastic carcinoma may not occur in cats at all (Table 1). One possible explanation for this difference between dogs and cats in the prevalence of various tumour types is that the dog breathes either through the nose or through the mouth, whereas the cat respires only through the nose. The scarcity of feline epidermoid tumours and the absence of small cell anaplastic carcinoma in cats may shed some light on the etiology of these two types of tumour, which are common in man. Perhaps the situation regarding the types of lung tumour encountered in animals now is similar to that seen in man a hundred years ago.

HISTOLOGICAL CLASSIFICATION AND NOMENCLATURE OF TUMOURS OF THE LUNG

I. EPIDERMOID CARCINOMA

II. ANAPLASTIC CARCINOMA

A. SMALL CELL ANAPLASTIC CARCINOMA
   1. Lymphocyte-like type (oat cell carcinoma)
   2. Fusiform type
   3. Polygonal type

B. LARGE CELL ANAPLASTIC CARCINOMA
   1. Giant cell type

III. ADENOCARCINOMA

A. PAPILLARY

B. BRONCHO-ALVEOLAR (including lung adenomatosis of sheep)

IV. COMBINED EPIDERMOID AND ADENOCARCINOMA

V. CARCINOID TUMOURS

VI. BRONCHIAL GLAND TUMOURS

VII. MIXED TUMOURS

VIII. BENIGN TUMOURS

IX. SARCOMAS

X. UNCLASSIFIED TUMOURS

DESCRIPTION OF TUMOURS

I. EPIDERMOID CARCINOMA

Epidermoid carcinoma (squamous cell carcinoma) (Fig. 1, 2) consists of solid masses of large cells showing varying degrees of stratification, keratinization, and flattening. The presence of intercellular bridges and/or keratinization is essential for this diagnosis. The tumour may have a uniform structural pattern throughout or may show more than one pattern. The most easily recognized pattern is of solid branching cords of cells showing varying degrees of differentiation to stratified squamous epithelium; a whorled effect is produced when the cords are sectioned transversely to their long axis. Some tumours of this group consist in part of solid islets and sheets of large cells with lightly stippled nuclei, resembling cells of the stratum spinosum of the skin. Scattered throughout the nonkeratinized forms there may be small pseudolumina containing eosinophilic proteinaceous material that does not stain for mucin. Because of these pseudolumina, the designation " adenoacanthoma " has been used. We prefer to retain the prefix " adeno-" for glandular tumours with true lumina.

Macroscopically, these tumours are white firm masses obviously located close to the hilus. This tumour is extremely rare in animals. We have encountered 4 canine cases, one feline case, and one bovine case. Coughing, emaciation, and hydrothorax are usually mentioned in the clinical reports. Metastases have been observed in the bronchial lymph nodes.

II. ANAPLASTIC CARCINOMA

In a tumour classification based strictly on histological criteria, there is little reason to separate the small cell anaplastic pulmonary carcinoma from the large cell lung carcinoma. Both tumour groups are only slightly differentiated, i.e., anaplastic in nature. In human lung tumours, the large cell carcinoma and the small cell carcinoma are listed in separate groups because their clinical behaviour and epidemiology are different. In animals these two criteria have not been investigated thoroughly because anaplastic carcinomas are very rare—the only species in which we have seen examples of this tumour is the dog. There are cases in which a diagnosis of anaplastic carcinoma could be made, but further subdivision into one of the subtypes described below may be debatable.

A. *Small cell anaplastic carcinoma*

These tumours are formed by masses of loosely packed cells, which do not touch one another. The stroma is predominantly delicate and does not completely separate the cell masses into distinct lobules. Occasional coarse strands of stroma are formed and often cell masses are seen penetrating into these strands. Larger tumour islets usually show central necrosis and this may superficially resemble keratinized debris, leading to a false diagnosis of epidermoid carcinoma. The surviving bronchiolar epithelium of the region may show hyperplasia and metaplasia. There is no clear-cut topographical evidence of a bronchial or bronchiolar origin. These neoplasms are highly invasive, sometimes with tumour plugs visible within the alveoli, blood vessels, and lymph vessels. Obviously, these tumours metastasize widely *via* the bloodstream and/or the lymphatic stream.

Clinically, these small cell anaplastic carcinomas behave malignantly. In all cases seen in the dog there was spread to the corresponding lymph nodes. There were also some haematogenous metastases. Dogs suffering from this tumour are usually emaciated. Generally, this type of tumour is encountered in younger animals, in contrast to other types of pulmonary carcinoma. The neoplasm may be situated in the hilus or in the central parts of the lobe, but we did not record any case in the periphery of the lobe.

We encountered three types of small cell anaplastic carcinoma, as described below.

1. *Lymphocyte-like type (oat cell carcinoma)* (Fig. 3). This extremely rare tumour consists of islets of round, lymphocyte-like cells with small, round, dense nuclei and a thin rim of cytoplasm. The epithelial nature of this type of tumour can best be recognized at the periphery of the tumour islets. Most often, there is a distinct invasion of the stroma. Occasionally, the tumour cells are located in the alveolar lumina and they may invade the lymph vessels and blood vessels. The stroma is delicate and irregular. There are necrotic areas and some inflammatory foci.

2. *Fusiform type* (Fig. 4, 5). Most of the canine cases of small cell anaplastic carcinoma consist of tumour masses separated by a delicate stroma into irregular neoplastic islets of varying size. The cells have spindle-shaped or oval, dense nuclei and moderate amounts of irregular or ovoid cytoplasm. We have seen one tumour that was a fusiform small cell anaplastic carcinoma with foci of epidermoid carcinoma. Such a tumour must be classified as an epidermoid carcinoma, in accordance with the rule that the most highly differentiated cells determine the classification.

3. *Polygonal type* (Fig. 6). There are no basic differences between this subtype and the lymphocite-like anaplastic carcinoma, except that the cytoplasm of the tumour cells is clearly visible but smaller in amount than that of the anaplastic large cell carcinoma. The shape of these cells is irregular. Giant cells, however, are lacking.

B. *Large cell anaplastic carcinoma*

These rare pulmonary neoplasms have been encountered in the dog but not previously described. In man, this type of tumour forms a separate entity, since its clinical behaviour and epidemiology are specific. The tumour cells are poorly differentiated and may form irregular cords. There is no evidence of an epidermoid structure. Occasionally, there is an indication of a gland-like pattern. In animals, we have not encountered the solid pleomorphic type, but we have seen several cases of the giant cell type.

1. *Giant cell type* (Fig. 7). This rare tumour has been encountered only in the dog. The cytoplasm is larger than in the polygonal cell type of the small cell anaplastic carcinoma. The cells are very pleomorphic. Often, there are multinucleate giant cells. No keratinization is visible and the cells are often arranged as in a sarcoma.

From the clinical point of view, this is a malignant tumour. We have observed metastases not only in the bronchial lymph nodes but also in the

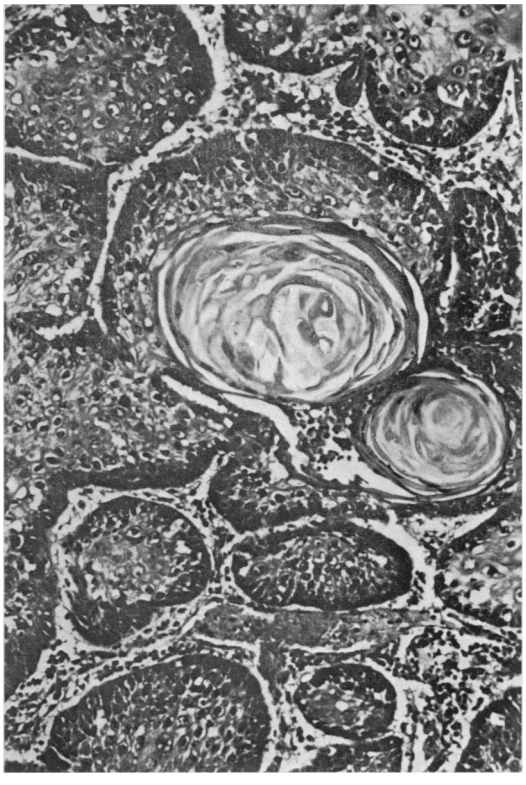

Fig. 1. Epidermoid carcinoma (dog).

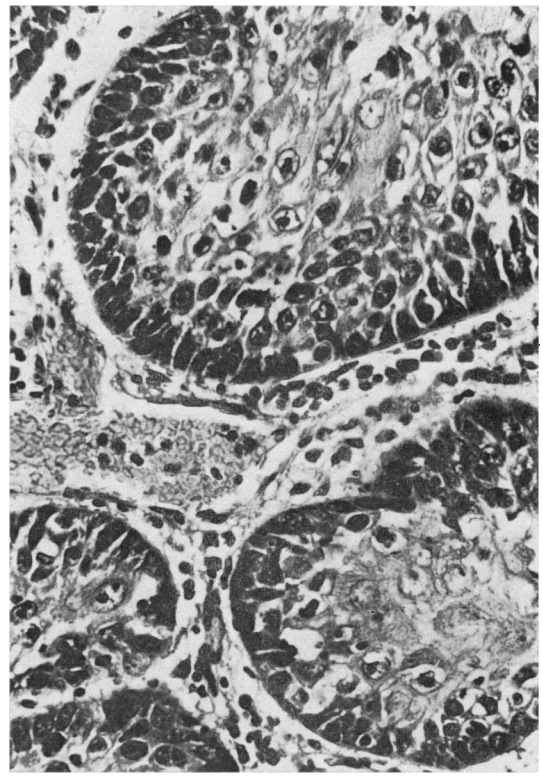

Fig. 2. Epidermoid carcinoma (dog).

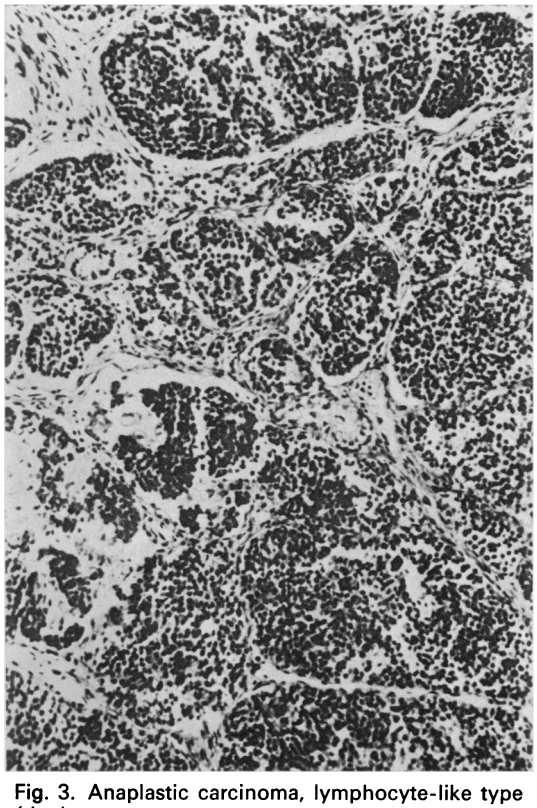

Fig. 3. Anaplastic carcinoma, lymphocyte-like type (dog).

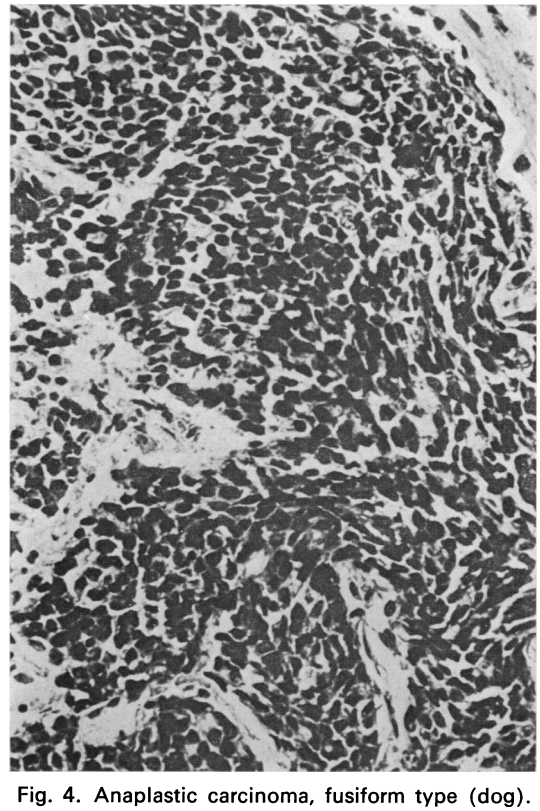

Fig. 4. Anaplastic carcinoma, fusiform type (dog).

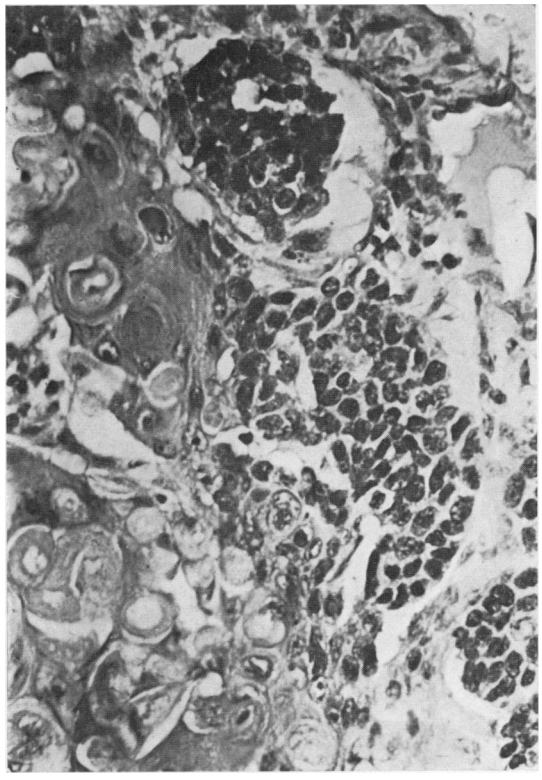

Fig. 5. Epidermoid carcinoma with anaplastic focus (dog).

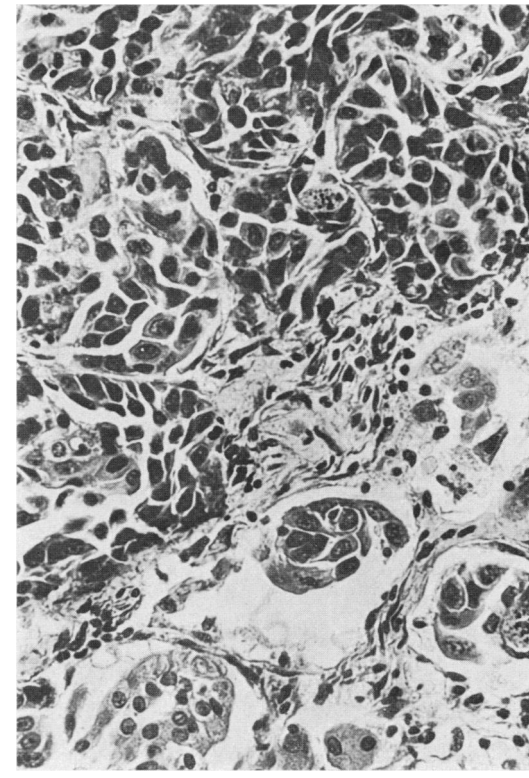

Fig. 6. Anaplastic carcinoma, polygonal type (dog).

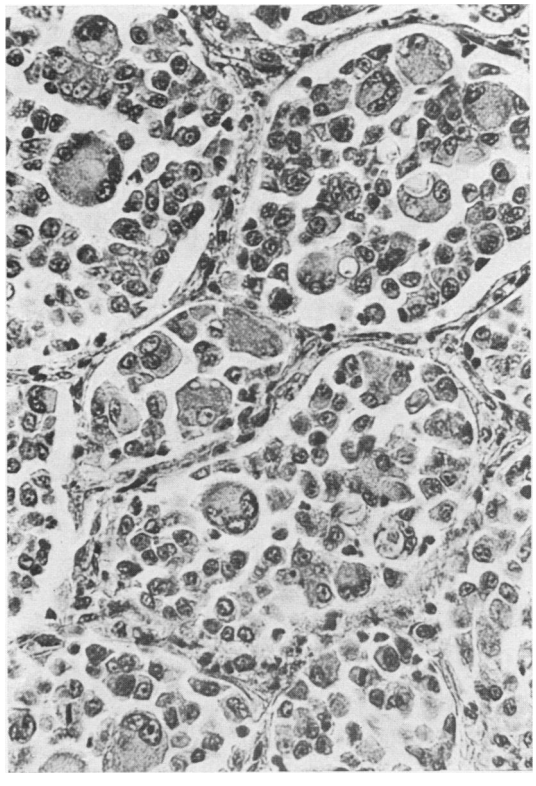

Fig. 7. Large cell anaplastic carcinoma, giant cell type (dog).

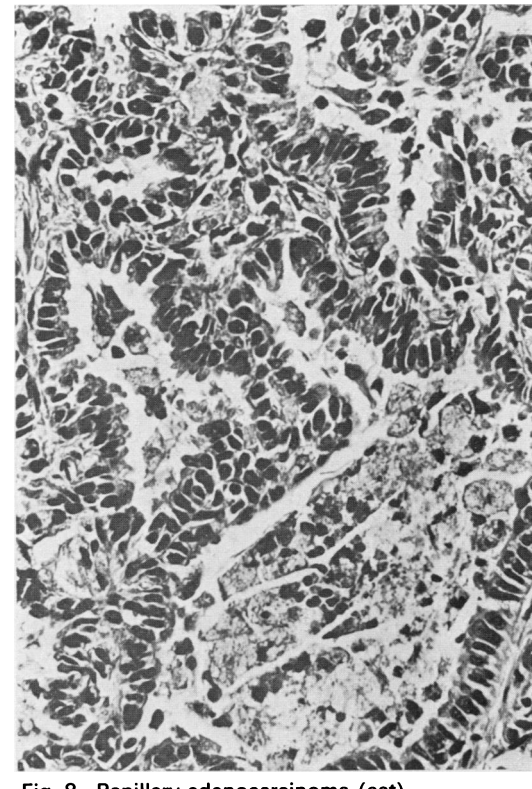

Fig. 8. Papillary adenocarcinoma (cat).

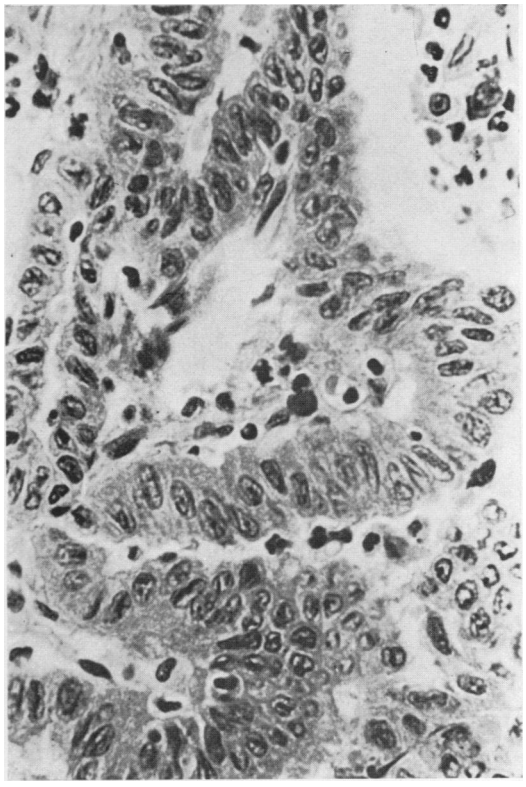

Fig. 9. Papillary adenocarcinoma (dog).

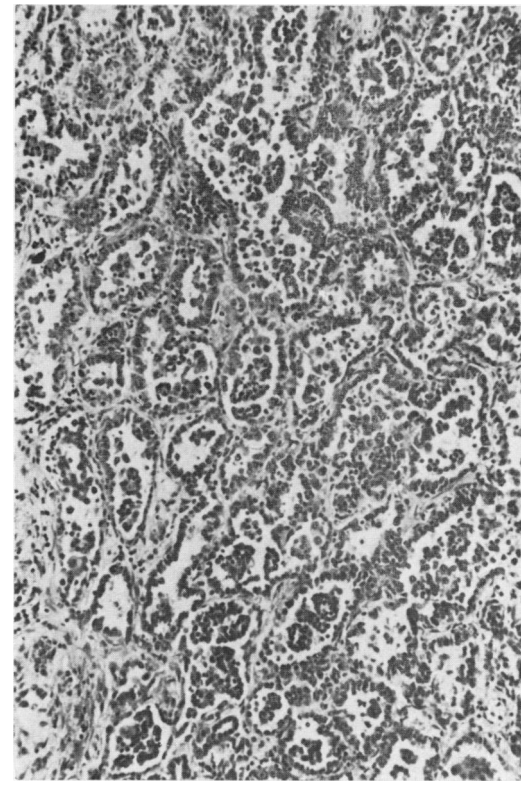

Fig. 10. Bronchiolo-alveolar adenocarcinoma (cat).

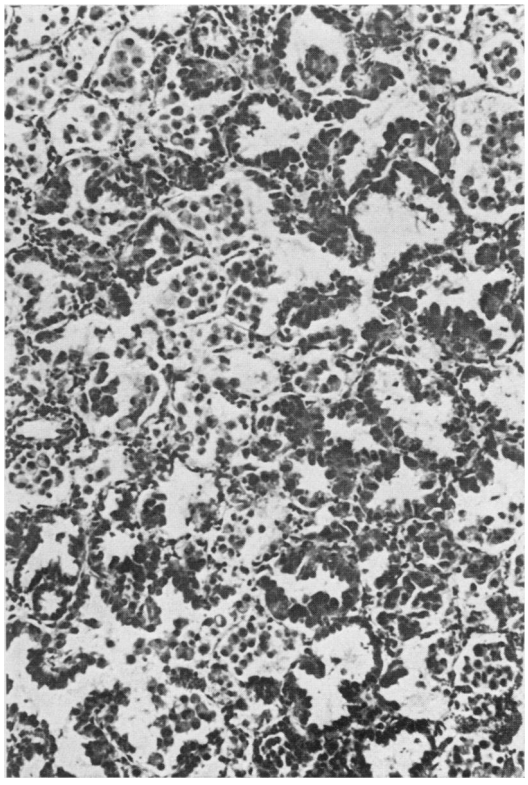

Fig. 11. Bronchiolo-alveolar carcinoma, lung adenomatosis (sheep).

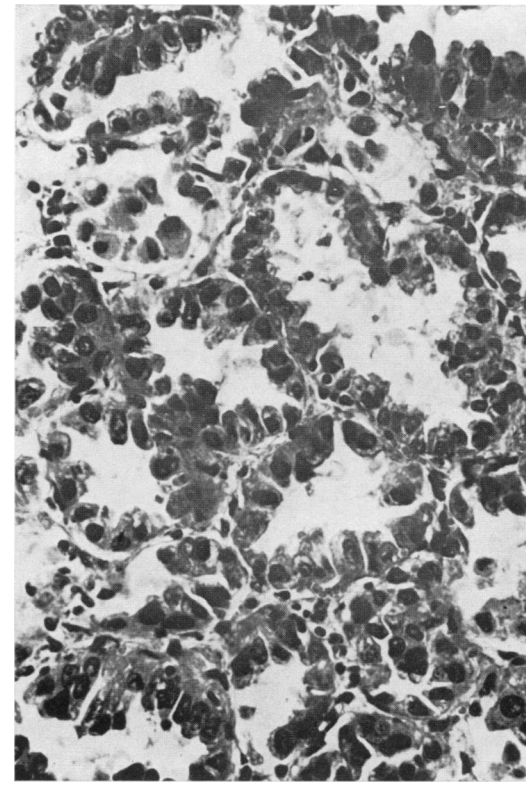

Fig. 12. Bronchiolo-alveolar carcinoma, lung adenomatosis (sheep).

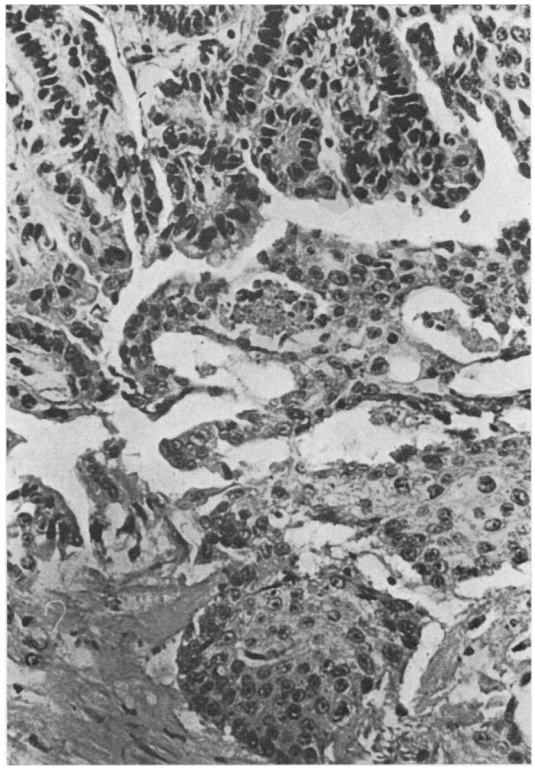

Fig. 13. Combined epidermoid and adenocarcinoma (dog).

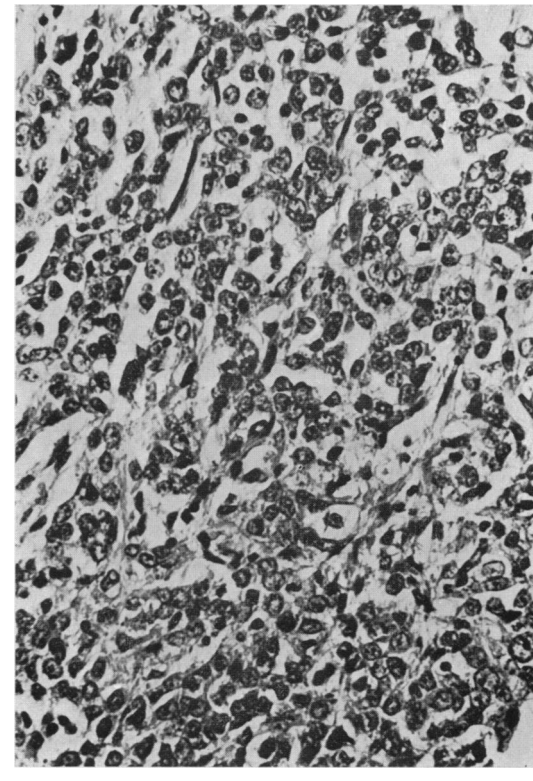

Fig. 14. Carcinoid of bronchus (dog).

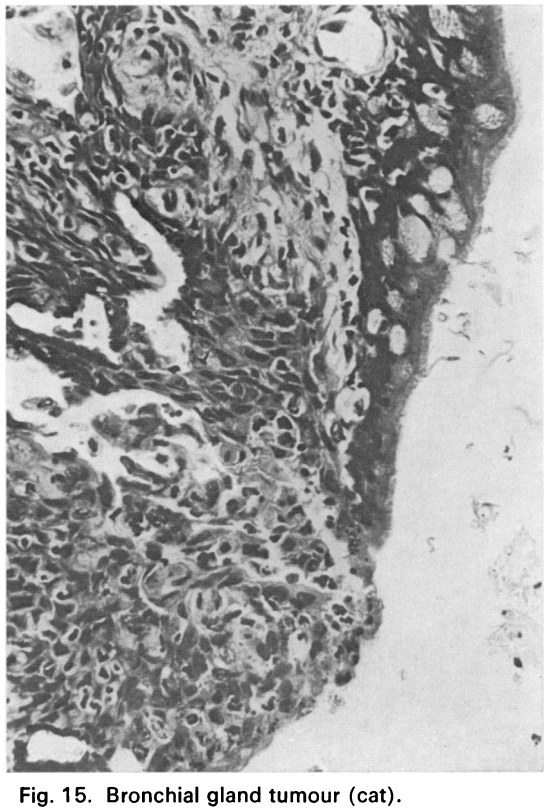

Fig. 15. Bronchial gland tumour (cat).

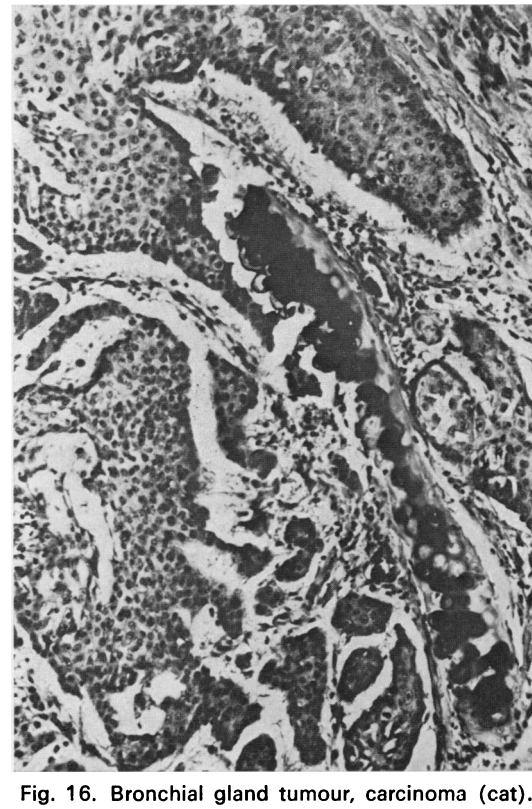

Fig. 16. Bronchial gland tumour, carcinoma (cat).

brain. According to Kreyberg et al. (2), the clear cell carcinoma in man probably has no counterpart in animals. These histologically different groups of anaplastic carcinoma obviously are closely related. Morphologically, the varying degree of differentiation is decisive. We have not encountered differences in clinical behaviour or in the degree of malignancy. The need for subdividing anaplastic carcinoma in animals into these histological entities is debatable.

III. ADENOCARCINOMA

The cells form tubules of gland-like structures in parts of the tumour. Adenocarcinoma can be classified either according to the type of epithelium (columnar or cuboidal) or according to the architecture. Since we have often found cuboidal and columnar (cylindrocellular) epithelium in the same neoplasm, we prefer a classification based on architecture. Two types of adenocarcinoma can be distinguished—papillary and bronchiolo-alveolar, the former being more common.

Very high papillary structures are often found beneath the pleura. We did not find clear-cut topographical evidence of a bronchial origin, judging by the remnants of cartilage plates and muscle coat of the bronchus of origin. In other words, we found no case of a tumour that could be classified as a bronchogenic tumour, as is understood by the term in human pathology.

Both subtypes of adenocarcinoma often infiltrate the whole lobe, macroscopically mimicking pneumonia. These tumours are located peripherally and frequently contain greenish gelatinous masses on cut surfaces.

In the domestic animals studied, adenocarcinoma represents by far the most frequent type of primary lung tumour. Pulmonary adenocarcinomas are generally very malignant; intrapulmonary metastases in several lobes, in the bronchial lymph nodes, in the pleura, and even in the brain are not uncommon. Clinically, these neoplasms are associated with coughing, dyspnoea, and sometimes fever due to secondary infections.

Pulmonary osteoarthropathy may be observed in the dog. There is no predilection according to sex or breed. The average age of dogs and cats with pulmonary adenocarcinoma is 12 years.

A. *Papillary* (Fig. 8, 9)

The papillary adenocarcinoma is the most common type of primary lung tumour in domestic carnivora and ruminants. The papillary structures may be exaggerated, especially in portions of the tumour immediately beneath the pleura pulmonalis. Such an exaggerated papillary mass may present some extremely complex patterns of transverse and tangential sections of the papillary fronds. Sometimes the papillary masses disintegrate and undergo varying degrees of necrosis, leaving a mass of cellular or amorphous debris with varying numbers of inflammatory cells. The height of the epithelium varies. In most cases the cells are columnar with large ovoid basal nuclei. Occasionally there are extremely tall epithelial cells with basal vacuoles that may or may not contain mucinous material. In a few cases these epithelial cells show cilia. Apices of cytoplasm occasionally protrude into the lumina, resembling the Clara cells of the rabbit. Mucin production is limited to some areas. The mucus is situated either within the epithelial cells or in the lumina. It is not known if the mucus secretion comes from the tumour cells or is produced in more normal areas of the lung and is merely retained by the tumour. The amount of mucus estimated by the macroscopic examination of the cut surface does not always correspond to the amount found histologically. In some cases, we have seen a cuboidal cell pattern, either combined with cylindrocellular areas or as a uniform cuboidal cell proliferation. These cuboidal cell tumours are well differentiated and show monotonously uniform papillary tumour proliferations. The cytoplasm is scanty and the nuclei are dense.

Usually there is only a limited infiltration of the surrounding alveoli. Plaques of tumour cells may be observed in lymphatic vessels and even in bronchiolar lumina, but are rare in blood vessels. In the apparently normal lung surrounding tumour foci, we often found small metastatic tumour plugs on histological examination. Central ischaemic necrosis, often with cholesterol clefts, and a limited dystrophic calcification were frequent.

The stroma of the papillary adenocarcinoma may show metaplasia to cartilage and even bone. This bone and cartilage tissue may be abundant but never neoplastic in nature. We have not yet encountered a true primary " mixed tumour " in animal lungs.

B. *Bronchiolo-alveolar* (Fig. 10–12)

This histological type is characterized by an alveolar pattern. The neoplastic epithelial cells infiltrate the laveolar spaces, mimicking glandular structures. The size and shape of the cells vary, and occasionally there are slight papillary formations in

some areas. The bronchiolo-alveolar type and the papillary type obviously are closely related tumours. Very little stroma is present, the tumour cells being placed on delicate fibrous septa. Necrotic areas are frequent. Invasive growth into the surrounding lung tissue is frequent, as are metastases to bronchial lymph nodes. Inflammation and metaplasia of the stroma to cartilage and bone may be present.

This subtype is rare in carnivora but frequent in sheep (lung adenomatosis of sheep, jaagziekte). The earliest lesions are found in alveoli or terminal bronchioles. The dorsal borders of the diaphragmatic lobes are the most frequently involved. The developed lesion in the sheep is similar to that in the dog and cat. The alveolar lumina at the junction of the tumour and normal lung are frequently filled with clusters of swollen alveolar macrophages—not a common phenomenon in dogs and cats.

Epidemiologically, this condition behaves like an infectious disease and may be associated with a virus. Cases occur in sheep aged from 9 months to 10 years, with a modal age of 3 years. Metastases to the bronchial lymph nodes occur in only about 4% of the sheep that die from the disease. For this reason we think that such cases should continue to be designated " adenomatosis ".

IV. COMBINED EPIDERMOID AND ADENOCARCINOMA

Combined epidermoid and adenocarcinoma (adenosquamous carcinoma) (Fig. 13) is the appropriate classification when these two main but related types of tumour are present in the same neoplasm. The two types of tumour must have reached a considerable degree of differentiation and extent. If one type clearly predominates, the tumour is classified as belonging to the predominant type, with mention of the other type present. The problems inherent in the use of the term " combined tumour " have been set out by Kreyberg el al. (2). We found that in dogs and cats combined tumours were rare. Several sections of a tumour should be examined before the diagnosis " combined tumour " can be made. We have no evidence that a tumour composed of two equally differentiated types of cell behaves in the same way as a tumour showing only one cell type.

As in man, the primary combined tumours in the lungs of animals are composed of an adenocarcinoma with an epidermoid carcinoma. As we did not have an opportunity to make a thorough study of metastases in such cases, we do not know whether both of these types of tumour metastasize. The borderline between a true combined lung tumour and an " adenocarcinoma with epidermoid metaplasia " may be debatable.

V. CARCINOID TUMOURS

Carcinoid tumours (Fig. 14) consist of polygonal cells with broad, slightly granular cytoplasm and a round or polygonal nucleus. These cells form either cords a few cells wide or larger solid masses separated by a delicate stroma with many blood vessels. These mosaic and trabecular patterns may be found in the same tumour. In some areas, a whorl-like arrangement of the polygonal cells may suggest an endocrine tumour. There has usually been extensive necrosis. Some of the tumour cells may contain minute argyrophilic granules in the cytoplasm.

Carcinoids in the canine lung have been found as large, firm, pale nodules localized in the immediate neighbourhood of a main bronchus. Metastases were present in the bronchial lymph node in both our canine cases. In addition, in one case, there was an extensive metastasis in the brain, which produced severe neurological symptoms. Secondary lesions typical of carcinoids in man have not been found in other organs. We did not encounter any evidence for the term " bronchial adenoma ", formerly used in human medicine.

VI. BRONCHIAL GLAND TUMOURS

We have seen a few bronchial gland tumours (Fig. 15, 16) in the dog and cat. These tumours seem to occur more frequently in animals than in man. The diagnosis is based mainly on the particular localization. These tumours originate in the glands of the bronchial mucous membrane. Both serous and mucous bronchial glands are found in carnivora. The surface epithelium shows some metaplastic change, which, in extreme cases, may lead to keratinization and stratification. Bronchial gland tumours are predominantly epidermoid in nature. There may be a varying degree of keratinization, forming whorls of keratin. In other cases, especially in cats, keratinization is lacking. Under the main tumour mass, tongues of tumour tissue may be seen protruding between the cartilage plates into the peribronchial tissue. We think that these tumours originate in serous glands since the production of mucus cannot be established by special stains. In some areas, there are gland-like structures in addition to the epiderm-

oid structure. Usually several glands show neoplastic change. Care must be taken not to confuse tumours of the bronchial glands with lymphatic permeation along peribronchiolar lymphatics by a bronchiolar adenocarcinoma.

Macroscopically, the tumour masses are of varying size. Since most bronchial glands are found in the major airways, tumours of these glands are situated near the hilus of the lung. Metastases in the corresponding lymph nodes are frequent.

We have not encountered any case of mucoepidermoid tumour of the bronchial glands, as described in man by Kreyberg et al. (2).

VII. MIXED TUMOURS

We have not yet encountered a true pulmonary mixed tumour in an animal.

VIII. BENIGN TUMOURS

Benign pulmonary tumours are very rare. Besides a fibroma and a myxochondroma, we have observed two cases of plasmacytoma in the canine lung. We have also found small adenomas with a papillary pattern in old cats.

IX. SARCOMAS

Pulmonary sarcomas are very rare in animals. A few sarcomas of haematopoietic or neurogenic origin have been described in carnivora, mainly the dog. These tumours seem to have a wide age distribution and a varying localization within the lung.

X. UNCLASSIFIED TUMOURS

Unclassified tumours are primary neoplasms of the lung that cannot be included in any of the above-mentioned categories.

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